

ARTICAINE AND PARESTHESIA: EPIDEMIOLOGICAL STUDIES

Daniel A. Haas, DDS, PhD, FRCD(C),
FACD

ABSTRACT

Permanent paresthesia following a local anesthetic injection is a possible adverse event. Epidemiological studies have suggested that the 4% solutions used in dentistry, namely prilocaine and articaine, are more highly associated with this occurrence. This article reviews the epidemiological evidence regarding articaine and paresthesia.

Local anesthetics are very safe drugs. Even though this is a correct statement, adverse events occur simply due to the sheer volume of injections given. Dentists in the U.S. administer over 300,000,000 cartridges every year (Malamed, 2004). Thus, even rare events, such as permanent paresthesia, will be noted. The first study to suggest the possibility that articaine is more highly associated with paresthesia was published in 1995 (Haas & Lennon). Since that time the scientific literature has been slowly accumulating that considers the possibility that local anesthetic neurotoxicity itself can cause paresthesia. The purpose of this article is to review the epidemiological evidence for the association between articaine and paresthesia in dentistry.

PARESTHESIA

What is meant by paresthesia that results from an intraoral injection of local anesthetic? Paresthesia is part of a more general grouping of nerve disorders known as neuropathies. These may manifest as a total loss of sensation (i.e., anesthesia), a burning or tingling feeling (i.e., dysesthesia), pain to a normally non-noxious stimulus (i.e., allodynia), or increased pain to all stimuli (i.e., hyperesthesia). For the purposes of this article, the term paresthesia will be used to describe prolonged complete anesthesia or an altered sensation that persists beyond the expected duration of action of a local anesthetic injection. Paresthesia is a known risk from oral

surgical procedures and it is assumed that the cause in that case is direct trauma to the nerve. However, paresthesia can also occur following nonsurgical dentistry, when local anesthesia is achieved to permit operative dentistry or scaling. The majority of these cases are transient and resolve within eight weeks. Those that last beyond that time frame are usually considered irreversible. It is the latter that are clearly the main concern, as there is no definitive treatment of this neuropathy. The focus of this article is on the nonsurgical permanent paresthesias that occur in dentistry.

There are several proposed mechanisms for paresthesia following local anesthetic injection. These include hemorrhage into the neural sheath, direct trauma to the nerve by the needle with possible scar tissue formation, and neurotoxicity of the local anesthetic. Only if the latter mechanism is correct could one find potential differences based on the type or the amount of local anesthetic used.



Dr. Haas is Associate Dean, Clinical Sciences, Faculty of Dentistry, Chapman Chair in Clinical Sciences, Professor and Head of Dental Anesthesia, Department of Pharmacology, Faculty of Medicine, University of Toronto, and Active Staff, Sunnybrook Health Sciences Centre. He can be reached at daniel.haas@utoronto.ca

There are several proposed mechanisms for paresthesia following local anesthetic injection. These include hemorrhage into the neural sheath, direct trauma to the nerve by the needle with possible scar tissue formation, and neurotoxicity of the local anesthetic.

Epidemiological Studies

Articaine has been available in Germany since 1976 and in Canada since 1983. In 1995, there was a publication of a retrospective study conducted to look at the incidence of permanent paresthesia from 1973 to 1993 inclusive in Ontario, Canada (Haas & Lennon, 1995). The database accessed was from the group that administered malpractice insurance to all licensed dentists in that province. At the time of the study there were approximately 6,200 dentists in Ontario. Only prolonged (i.e., permanent) paresthesia from nonsurgical cases was counted in this study. The conclusion was that there was an overall incidence of one irreversible paresthesia out of every 785,000 injections. Compared with the other local anesthetics, a higher incidence was noted when articaine or prilocaine were used. The lingual nerve was involved in 64% of the cases, with the inferior alveolar nerve involved in the vast majority of the remainder. There was no association with any other factor, such as needle gauge.

A follow-up study was done using the same methodology with the data from 1994 to 1998 inclusive (Miller & Haas, 2000). For this time period, the incidence of nonsurgical paresthesia in dentistry was 1:765,000, very similar to the previous finding. The conclusions were the same in that prilocaine and articaine were more commonly associated with this event compared to the other local anesthetics. The lingual nerve was involved in 70% of the cases, with the inferior alveolar involved in the vast majority of the remainder. It was estimated that the incidence of permanent paresthesia from either prilocaine or articaine approximated 1:500,000 injections for each drug, which was five-fold higher than that found with

lidocaine or mepivacaine. In both studies, there were no reports of paresthesia from bupivacaine.

The reasons for these findings were speculative. What articaine and prilocaine have in common is that they are the only 4% solutions used in dentistry. This means that the concentration of the drug is 40 mg per mL. The other agents available in dental cartridges in the U.S. and Canada are all more dilute. Lidocaine is a 2% solution, mepivacaine is either 2% or 3%, and bupivacaine is 0.5%. This led to the consideration that it was not the specific drug that was the factor, but maybe the concentration administered.

IN VITRO STUDIES

Is there evidence for a dose-dependent neurotoxicity of local anesthetics? Several in vitro studies support this hypothesis. As early as 1976, it was noted that rats injected with lidocaine at the trigeminal ganglion exhibited inhibition of rapid axonal transport in distal nerve segments in a dose-dependent manner (Fink & Kish, 1976). An investigation of the effects of lidocaine on resting membrane potentials and action potentials in single crayfish giant axons showed a dose-dependent effect resulting in irreversible conduction blockade with complete loss of resting membrane potential at higher doses (Kanal et al., 1998). High concentrations of local anesthetics, such as 5% lidocaine, have been shown to result in irreversible conduction block, an effect not found with 1.5% lidocaine (Lambert et al., 1994).

Histologic studies have primarily supported the hypothesis that local anesthetics have neurotoxic potential (Kalichman et al., 1989; 1993), although one study using microinjections into rat sciatic and cat lingual nerves showed no significant effect (Hoffmeister et al., 1991). This latter study, however, suffered from a potential methodologic problem of using no control group, using a

sample size of five for each group, and injecting only twenty microliters of local anesthetic into the rat sciatic nerve. Conversely, the opposite findings to this latter study were shown when a saline control group was used, the sample size increased to sixteen, the volume injected in the rat sciatic nerve was increased to fifty microliters, and the effects assessed electrophysiologically (Cornelius et al., 2000).

In a study investigating neuronal cytoplasmic calcium concentrations and neuronal cell death, it was shown that lidocaine in concentrations less than 1% caused minimal changes, whereas 2.5% and, to a greater degree, 5% lidocaine caused much larger changes and cell death (Johnson et al., 2002). When the concentrations were kept the same, lidocaine and prilocaine had equivalent neurotoxicity in rats (Kishimoto et al., 2002). In a study looking at lidocaine, mepivacaine, bupivacaine, and ropivacaine, all of these local anesthetics produced growth cone collapse and neurite degeneration (Radwan et al., 2002), suggesting that neurotoxicity is not restricted to one agent. A proposed mechanism for this irreversible nerve injury is membrane disruption, characteristic of a detergent effect (Kitagawa et al., 2004). Other studies also support the hypothesis that all local anesthetics have the potential for neurotoxicity, an effect that is dose-dependent (Selander, 1993; Kalichman, 1993).

Clinical Studies

Articaine was introduced in the U.K. in 1998. Since that time a number of letters to the editors of British journals reported an apparent increase in prolonged paresthesia following articaine administration (van Eiden & Patel, 2002; Pedlar, 2003). A follow-up letter identified only a small

number of official reports regarding articaine and paresthesia with the U.K. Committee on Safety of Medicines and asked dentists to use this reporting system as required (Randall, 2003).

Articaine's introduction into the U.S. in 2000 coincided with a publication of its efficacy (Malamed et al., 2000), and shortly thereafter followed by a publication on its safety (Malamed et al., 2001). These two studies were based on the findings from a multi-center randomized controlled trial (RCT) on 1,325 subjects comparing administration of 4% articaine with 1:100,000 epinephrine to 2% lidocaine with 1:100,000 epinephrine. The study on efficacy showed that articaine was comparable to lidocaine for mandibular blocks, a finding replicated in RCTs published since that time (Malamed et al., 2000; Claffey et al., 2004; Mikesell et al., 2005; Ram & Amir, 2006). The study on safety concluded that the adverse event profile was similar to that found with lidocaine.

A prospective study of nonsurgical permanent paresthesia conducted in the U.S. just prior to articaine's release found that lidocaine was the drug used in 48% of the cases and prilocaine in 47% of the cases when the type of drug was known (Pogrel & Thamby, 2000). They estimated that, at the time of their writing, lidocaine accounted for 62% of all local anesthetics used by dentists and prilocaine accounted for 13%. This higher proportion for prilocaine was consistent with that previously reported (Haas & Lennon, 1995). The authors also determined that 79% of the cases involved the lingual nerve, a finding also consistent with that reported previously by Haas and Lennon. It was estimated that the overall incidence of permanent paresthesia for each inferior alveolar nerve block ranged from 1:26,762 to 1:160,571. Malamed and colleagues concluded that "Perhaps every full-time practitioner will find that he or she has

one patient during his or her career who has permanent nerve involvement resulting from an inferior alveolar nerve block."

One interesting question is why is the lingual nerve the most common nerve affected? To answer this, an elegant study published in 2003 examined the histologic characteristics of lingual nerves in twelve cadavers (Pogrel et al.). This study showed a range in the number of fascicles present within this nerve; anywhere from one to eight inclusive. Four of them (33%) had only one fascicle. The authors speculated that a unifascicular nerve may be injured more easily than one with multiple fascicles. To date, this appears to be the most plausible explanation for the finding of the predilection of the lingual nerve for permanent paresthesia.

In 2003, a review of paresthesia associated with administration of local anesthetics was published (Dower, 2003). This review analyzed previous studies (Haas & Lennon, 1995; FDA, 1998; Miller & Haas, 2000; Malamed et al., 2000; 2001; CRA, 2001) and by making a number of alternative assumptions determined an incidence of paresthesia for articaine of 1:220,000—higher than that previously reported. Specifically, it was stated that articaine had a twenty-fold higher rate of paresthesia than lidocaine and that prilocaine had a fifteen-fold higher incidence. Articaine's rate for paresthesia for lingual or mandibular blocks was estimated to be as high as 2% to 4% when used for mandibular or lingual blocks.

It appears that it is not the drug per se that is responsible, but simply the higher concentration that predisposes these formulations to this possibility.

Articaine was introduced in 2000 in Denmark. Recently, a Danish study (Legarth, 2004) was conducted that used a format similar to the one carried out by Haas and Lennon in Canada in 1995. Using data from the Danish Dental Association's Patient Insurance Scheme, the author reviewed reports of paresthesia from 2002-2004 in that country. In this time period, thirty-two lingual nerve injuries were registered. Articaine was given in 88% of the cases, even though it constituted only 42% of the market. Mepivacaine, as the 3% formulation, was given in the other 12% of cases, and it constituted 22% of the market. Lidocaine, with 22% of the market, had no reports of paresthesia. Prilocaine had 12% of the market, and no reports of paresthesia. Interestingly, in Denmark, prilocaine is formulated as a 3% solution, not 4% as found in the U.S. and Canada. This incidence of paresthesia was 1:140,000 for articaine and 1:540,000 for mepivacaine.

Another recent publication used standardized tests of neurosensory function to determine the cause of injection injury to the oral branches of the trigeminal nerve (Hillerup & Jensen, 2006). This prospective study of fifty-six consecutive patients demonstrated neurologic evidence of neurotoxicity, not mechanical injury, which resulted in irreparable damage. Consistent with previous clinical studies, the lingual nerve was the most common nerve involved, accounting for 81% of the cases, with the inferior alveolar nerve making up the rest. There was also a significant difference in the drugs associated with this neurologic injury. In these patients, articaine was shown to contribute to more than a twenty-fold increase in paresthesia compared to all other local anesthetics combined. The authors noted a substantial increase in the number of injection injuries since

articaine was introduced into the Danish market.

The conclusions of these authors were subsequently questioned in a letter to the editor, pointing out that the paresthesias almost exclusively involved the lingual nerve during a traditional mandibular block and rarely other nerves or other blocks (Malamed, 2006). Yet, this letter did not explain why articaine was still the most common local anesthetic associated with the damage of this one nerve compared with other agents that are also used to block this nerve. Furthermore, Hillerup and Jensen demonstrated that their neurological assessment demonstrated neurotoxicity and not mechanical injury. As well, the statement in the letter, "At this time there exists absolutely no scientific evidence to support the concluding comment regarding the use of other local anaesthetics for mandibular block analgesia in place of articaine 4%," could be considered to be not quite correct. While it is true that no RCT has made this demonstration, a number of other scientific studies have, be they prospective (Hillerup & Jensen 2006) or retrospective (Haas & Lennon, 1995). RCTs are not the only scientific studies used to guide clinical decision making, as will be discussed below.

Most recently, in the U.S., two new RCTs were published that compared the formulations of articaine with different concentrations of epinephrine: 1:100,000 and 1:200,000, investigating cardiovascular effects (Hersh et al., 2006) and efficacy (Moore et al., 2006). The sample sizes were 14 and 126, respectively, and no differences in adverse events were noted between

the two formulations of articaine with epinephrine.

Clinical Application of the Evidence

How does the practicing dentist make use of this information? Should a dentist wait for the publication of a RCT proving that articaine and prilocaine are more likely to cause permanent paresthesia than other local anesthetics? Because of the rarity of this event, elucidation of these local anesthetic risk factors is statistically problematic, a finding that has occurred elsewhere in the field of anesthesiology (Hopwood, 1993). With incidences estimated to be anywhere from 1 in 26,700 (Pogrel & Thamby, 2000), 1 in 140,000 (Legarth, 2004), 1 in 220,000 (Dower, 2003), to 1 in 785,000 (Haas & Lennon, 1995), it would take an unrealistically large RCT to detect a statistically significant difference. The largest RCT on articaine published to date had a sample size of only 1,325 (Malamed et al., 2000), far too small to be able to detect a statistically significant difference if one were to exist. None of the RCTs involving articaine or prilocaine published to date has a sample size large enough to detect this potential difference. No conclusions regarding permanent paresthesia should be made from these particular studies. To quote Hillerup and Jensen (2006), "Since the incidence of injury as such is extremely rare, the finding of nerve injury in a clinical trial is comparable with the finding of a needle in a haystack." Given this reality, they go on to say, "This feature imposes a methodological obstacle to the power of conclusion from prospective clinical studies on injection injuries, and circumstantial evidence, experimental research and retrospective surveys on great number of patients must be taken into account."

Conclusion

In conclusion, the scientific data are strongly suggestive that the 4% local anesthetic solutions used in dentistry, namely articaine and prilocaine, are associated with an increased likelihood of permanent paresthesia. It appears that it is not the drug per se that is responsible, rather the higher concentration that predisposes these formulations to this possibility. This outcome most often involves the tongue, and can leave the affected patients with an incapacitation for the rest of their lives.

Dentists must always take into account the risks and benefits when determining the appropriateness of every procedure and therapeutic decision. In 2005 the Royal College of Dental Surgeons of Ontario, the governing body for dentists in that province, published an advisory to its members and concluded, "Until more research is done, it is the College's view that prudent practitioners may wish to consider the scientific literature before determining whether to use 4% local anaesthetic solutions for mandibular block injections." (Royal College of Dental Surgeons of Ontario, 2005) Their conclusion is warranted. Unless there is evidence of a demonstrable benefit to the use of these particular drugs, their risks make their selection difficult to justify for mandibular or lingual blocks. Today, unless extenuating circumstances are present, the available epidemiological evidence appears to support a dentist's decision to avoid the use of articaine and prilocaine for mandibular and lingual blocks, and to restrict their use to other injections. ■

REFERENCES

- Claffey, E., Reader, A., Nusstein, J., Beck, M., & Weaver J. (2004). Anesthetic efficacy of articaine for inferior alveolar nerve blocks in patients with irreversible pulpitis. *Journal of Endodontics*, 30, 568-571.
- Cornelius, C. P., Roser, M., Wietholter, H., & Wolburg, H. (2000). Nerve injuries due to intrafascicular injection of local anesthetics experimental findings. *Journal of Craniomaxillofacial Surgery*, 28 (suppl 3), 134-135.
- CRA Newsletter. (2001). Articaine HCl 4% with epinephrine 1:100,000—update '05. 29(6), 1-2.
- Dower, J. S. (2003). A review of paresthesia in association with administration of local anesthesia. *Dentistry Today*, 64-69.
- FDA Center for drug evaluation and research approval package for: Application number 20-971. (1998). *Statistical Review*, 1-19.
- Fink, B. R., & Kish, S. J. (1976). Reversible inhibition of rapid axonal transport in vivo by lidocaine hydrochloride. *Anesthesiology*, 44 (2), 139-146.
- Haas, D. A., & Lennon, D. (1995). A 21 year retrospective study of reports of paresthesia following local anesthetic administration. *Journal of the Canadian Dental Association*, 61, 319-330.
- Hillerup, S., & Jensen, R. (2006). Nerve injury caused by mandibular block analgesia. *International Journal of Oral Maxillofacial Surgery*, 35, 437-443.
- Hoffmeister B. (1991). Morphologic veränderungen peripherer nerven nach intraneuraler lokalanästhesieinjektion. *Dtsch Zahnarztl Z*, 46, 828-830.
- Hopwood, M. B. (1993). Statistics: Can we prove an association for a rare complication? *Regional Anesthesia*, 1, 428-433.
- Johnson, M. E., Saenz, J. A., DaSilva, A. D., Uhl, C. B., & Gores, G. J. (2002). Effect of local anesthetic on neuronal cytoplasmic calcium and plasma membrane lysis (necrosis) in a cell culture model. *Anesthesiology*, 97, 1466-76.
- Kalichman, M. W. (1993). Physiologic mechanisms by which local anesthetics may cause injury to nerve and spinal cord. *Regional Anesthesia*, 18, 448-452.

None of the RCTs involving articaine or prilocaïne published to date has a sample size large enough to detect this potential difference. No conclusions regarding permanent paresthesia should be made from these particular studies.

Kalichman M. W., Powell, H. C., & Myers, R.R. (1989). Quantitative histologic analysis of local anesthetic-induced injury to rat sciatic nerve. *Journal of Pharmacology and Therapeutics*, 250, 406-413.

Kalichman, M. W., Moorhouse, D. F., Powell, H. C., & Myers, R. R. (1993). Relative neural toxicity of local anesthetics. *Journal of Neuropathology and Experimental Neurology*, 52, 234-240.

Kanai, Y., Katsuki, H., & Takasaki, M. (1998). Graded, irreversible changes in crayfish giant axon as manifestations of lidocaine neurotoxicity in vitro. *Anesthesia Analgesia*, 86, 569-573.

Kishimoto, T., Bollen, A. W., & Drasner, K. (2002). Comparative spinal neurotoxicity of prilocaïne and lidocaine. *Anesthesiology*, 97, 1250-1253.

Kitagawa, N., Oda, M., & Totoki, T. (2004). Possible mechanism of irreversible nerve injury caused by local anesthetics. *Anesthesiology*, 100, 962-967.

Lambert L. A., Lambert, D. H., & Strichartz, G. R. (1994). Irreversible conduction block in isolated nerve by high concentrations of local anesthetics. *Anesthesiology*, 80, 1082-1093.

Legarth, J. (2005). Lesions to the lingual nerve in connection with mandibular analgesia. *Tandlaegebladet*, 109, 10.

Malamed, S. F. (2004). *Handbook of Local Anesthesia*. Mosby, 5th edition, 285.

Malamed, S. F. (2006). Nerve injury caused by mandibular block analgesia [letter]. *International Journal of Oral Maxillofacial Surgery*, 35, 876-877.

Malamed, S. F., Gagnon, S., & Leblanc, D. (2000). A comparison between articaine HCl and lidocaine HCl in pediatric dental patients. *Pediatric Dentistry*, 22, 307-311.

Malamed, S. F., Gagnon, S., & Leblanc, D. (2001). Articaine hydrochloride: a study of the safety of a new amide local anesthetic. *Journal of the American Dental Association*, 132, 177-185.

Malamed S. F., Gagnon, S., & Leblanc, D. (2000). Efficacy of articaine: a new amide local anesthetic. *Journal of the American Dental Association*, 131, 635-642.

Mikesell, P., Nusstein, J., Reader, A., Beck, M., & Weaver, J. (2005). A comparison of articaine and lidocaine for inferior alveolar nerve blocks. *Journal of Endodontics*, 31, 265-270.

Miller, P. A., & Haas, D. A. (2000). Incidence of local anesthetic-induced neuropathies in Ontario from 1994-1998 [abstract]. *Journal of Dental Research*, 79SI, 627.

Pedlar, J. (2003). Prolonged paraesthesia [letter]. *British Dental Journal*, 195, 119.

Pogrel, M. A., Schmidt, B. L., Sambajon, V., & Jordan, R. C. K. (2003). Lingual nerve damage due to inferior alveolar nerve blocks a possible explanation. *Journal of the American Dental Association*, 134, 195-199.

Pogrel, M. A., & Thamby, S. (2000). Permanent nerve involvement resulting from inferior alveolar nerve blocks. *Journal of the American Dental Association*, 131, 901-907.

Radwan, I. A. M., Saito, S., & Goto, F. (2002). The neurotoxicity of local anesthetics on growing neurons: a comparative study of lidocaine, bupivacaine, mepivacaine, and ropivacaine. *Anesthesia Analgesia*, 94, 319-324.

Ram, D., & Amir, E. (2006). Comparison of articaine 4% and lidocaine 2% in paediatric dental patients. *International Journal of Paediatric Dentistry*, 16, 252-256.

Randall, C. (2003). Anaesthetic solutions [letter]. *British Dental Journal*, 195, 482.

Royal College of Dental Surgeons of Ontario. (2005). Paraesthesia following local anaesthetic injection. *Dispatch*, 19, 26.

Selander, D. (1993). Neurotoxicity of local anesthetics: Animal data. *Regional Anesthesia*, 18, 461-468.

VanEden, S. P., & Patel, M. F. (2002). Letter to the editor: Prolonged paraesthesia following inferior alveolar nerve block using articaine. *British Journal of Oral and Maxillofacial Surgery*, 40, 519-520.